REMARKS/ARGUMENTS

35 USC §112, 1st paragraph

The Examiner has objected to former claims 19 to 22 alleging that the specification does not provide enablement for the *O. gratissimum* extract to inhibit the cytopathic effects, e.g. HIV viral replication, of a virus in a cell. In particular, the Examiner states:

> The claims as amended are not limited to the treatment of HIV infected cell *in vitro* [sic], the claims broadly interpreted can include the treatment of cells as they are found in an individual and for this the specification is not enabled. ... The specification does not provide sufficient guidance for the inhibition of a HIV viral infection in a patient with a *O. gratissimum*. There is not indication that high enough concentrations of the compound can be achieved in the patient to effect the viral replication *in vivo*. It is not a straightforward process to go from *in vitro* data to an *in vivo* treatment. Thus, the lack of working examples regarding treatment of HIV infection in a patient, the lack of guidance in the specification, and the unpredictability regarding extrapolating *in vitro* data to an *in vivo* treatment method greatly reduces the probability that one of skill in the art would successfully obtain the claimed invention without undue experimentation.

Applicant has carefully considered the Examiner's comments but respectfully disagrees that the invention as claimed contravenes 35 USC §112, 1st paragraph for lack of enablement and submits that the specification is sufficient to enable one skilled in the art at the time the application was filed to practice the method encompassed by the scope of the claims.

MPEP Section 2164.02, CORRELATION: IN VITRO/IN VIVO, provides that:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of

PAGE 4/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14

> use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). [Emphasis added.]
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

The Applicant submits that the application discloses an adequate "how-to-use" knowledge directed to the practical utility of the instant invention. Using art-accepted cell lines, the *in vitro* tests described in the application provide evidence and adequate proof regarding the pharmacological activity of the plant extracts to inhibit the cytopathic effects of virus-infected cells. Moreover, a skilled worker would be able to determine the relative strength or concentration of the plant extracts needed to achieve the pharmacological activity, i.e. to inhibit cytopathic effects of a virus-infected cell, *in vivo* without undue burden or experimentation. The state of the art at the time the application was filed demonstrates the predictability and certainty of practising the method with particular cell types, particularly with mammalian cells.

In vitro testing permits an investigator to establish the potency of a compound with respect to the particular pharmacological activity which can then be selected for further testing *in vivo*. *In vitro* testing, in general, is accepted practice in the pharmaceutical industry because it

PAGE 5/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14

is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation between them. As such, successful *in vitro* testing for a particular pharmacological activity establishes a significant probability that *in vivo* testing for the same pharmacological activity will likely be successful. The exemplified cell lines "Vero" and Molt-4 are well known and art-recognized model systems that provide characteristics suitable for testing the ability of the plant extracts to inhibit HIV production in chronically infected cells, thereby reducing HIV cytopathicity. (See also, for example, U.S. Patent No. 6,685,950, "Methods of Treating Viral Infections".)

The objective of the pharmaceutical research undertaken by the Applicant was to establish whether certain plant extracts have a particular pharmacological activity or practical utility. If the stated utility of the invention in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, then 35 U.S.C. §112 is satisfied. *In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). For example, it is not necessary to specify concentrations high enough to inhibit viral replication *in vivo* if such information could be obtained by a skilled person without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate concentration without undue experimentation, this would be sufficient to satisfy 35 U.S.C. §112, first paragraph. In the past, courts have recognized that determining effective concentration for a pharmaceutical agent against a particular disease is well with in the ordinary skill in the art, *In re Bundy*, 209 U.S.P.Q. 48 (C.C.P.A. 1981). Based on the disclosure of the instant invention and the state of the art, those skilled in the art had available, at the critical date, information as to approximate concentration levels for the plant extracts to inhibit the cytopathic effect of a virus-infected cell. The *in vitro* data provides sufficient information as an initial starting point so that one skilled in the art could determine, without inventive skill or undue experimentation, the necessary strength or concentrations of the plant extracts to achieve the desired pharmacological effect *in vivo*, i.e., the inhibition of HIV replication in mammalian or human cells. Moreover, the applicant need not demonstrate that the invention is completely safe. (MPEP Sections 2107 and 2164.01).

PAGE 6/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14

The question of enablement and utility are closely related. For example, in the decision *In re Brana (supra)* the Federal Circuit reversed a Board of Appeals decision upholding the Examiner's utility and enablement rejection of claims directed to compounds for use as antitumor agents. The applicants' specification disclosed that the claimed compounds were superior antitumor agents as compared to prior art compounds that had antitumor activity. The compounds were tested using *in vivo* animal tumor models that are used by the U.S. National Cancer Institute to determine whether a compound should be selected for further study. The Examiner rejected the application on the basis that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for testing in humans, and that these tests were not reasonably predictive of the success of the claimed compounds for treating cancer in humans. However, the Federal Circuit disagreed stating:

> Usefulness in patent law, and in particular in the context of pharmacological inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The court concluded that the applicants' disclosure complied with the requirements of 35 USC §112, first paragraph, and reversed the Board's decision.

In summary, it is submitted that the disclosure satisfies the enablement requirement of 35 USC §112, first paragraph since (1) working examples regarding the pharmacological activity of the plants extracts to inhibit the cytopathic effects of a virus-infected cells are provided, (2) adequate guidance to practice the invention is provided in the specification, and (3) the extrapolation of *in vitro* data to an *in vivo* method of use using art-recognized cell lines provides a significant probability that one of skill in the art would successfully obtain the invention as claimed without undue experimentation.

PAGE 7/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14

In view of the foregoing, Application respectfully submits that the disclosure of the instant invention satisfies the first paragraph of 35 USC § 112 and requests that the rejection be withdrawn.

Claim Rejections - 35 USC §102

The Examiner has reapplied El-Said *et al.* as anticipating the claimed subject matter on the grounds that the instant invention reads on the treatment of a viral infection *in vivo* using an extract of *Ocimum gratissimum*.

Applicant respectfully traverses the rejection.

MPEP §2131 provides that:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The **identical invention** must be shown in as complete detail as contained in the ... claim." [Emphasis added.] *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim.

MPEP §2121.01 also provides that:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel'or 'anticipated' within section 102, the stated test is whether a reference contains an **'enabling disclosure'** ... ." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). [Emphasis added.] A reference contains an enabling disclosure if the public was in possession of the claimed invention before the date of the invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

PAGE 8/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14

F. El-Said *et al.* disclose the chemotaxonomy and antibacterial testing of *Ocimum gratissimum* specimens collected from different areas around Ibadan, Western State of Nigeria. *Ocimum gratissimum* is known for its medicinal properties in the treatment of fever, as a diaphoretic, a stomachic and laxative.

At page 197, the authors describe the preparation and testing of (a) an aqueous extract of the whole plant, (b) the essential oil, and (c) an aqueous solution of the oil for their ability to inhibit growth of certain gram-negative and gram-positive organisms, including:

Gram-Negative		Gram-Positive
Escherichia coli	*Salmonella spp.*	*Bacillus subtilis*
Klebsiella aerogenes	*Shigella schmitzi*	*Sarcina lutea*
Proteus spp.	*Shigella sonnei*	*Staphylococcus aureus*
Pseudomonas aeruginosa		

Cultures of the various organisms where spread across a petri dish containing nutrient agar. The aqueous extract was contained in a "ditch" that was formed in the center of the agar. The essential oil was tested by placing small drops on the surface of the seeded agar plates. Aqueous dilutions of the oil were made in nutrient broth and inoculated with broth culture of the particular organism.

The instant specification discloses the testing of plant extracts against HIV, herpes viruses, and some other viruses that afflict mankind (see, for example, page 2, lines 26 to 31). The invention, as claimed, is not anticipated by F. El-Said *et al.* because the reference does not disclose anti-viral testing and/or a method of use of *Ocimum gratissimum* for inhibiting the cytopathic effects of a virus-infected cell. Bacteria are single-celled organisms, capable of

PAGE 9/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14

reproducing on their own. A virus is an infectious agent, smaller than bacteria, which requires the cells of a living organism to grow or reproduce.

Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the forgoing, early favorable consideration of this application is earnestly solicited.

Respectfully submitted,

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PAGE 10/10 * RCVD AT 11/9/2004 4:15:06 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/5 * DNIS:8729306 * CSID:+613 * DURATION (mm-ss):03-14